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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,558	03/25/2005	Ernst Hafen	27656/38365A	1027

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EXAMINER	
EMCH, GREGORY S	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,558	HAFEN ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II claims 6-12, in the communication dated July 8, 2005 is acknowledged. Currently, claims 6-12 are pending and under consideration.

Information Disclosure Statement

A signed and initialed copy of the IDS paper filed October 20, 2004 is enclosed in this action.

Claim Objections

Claim 9 is objected to as being dependent upon a non-elected base claim. Claim 9 recites the limitation "the nucleic acid sequence as defined in claim 2." Claim 2 is drawn to a non-elected invention and is therefore not currently pending. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6-12 are directed to a method for the identification of a hyperproliferative disease, in particular benign and malignant tumors, or a genetic predisposition thereof, which comprises detecting in a body fluid or a tissue sample of a subject a change in the expression level of an ELP protein or at least one mutation within a nucleic acid sequence encoding an ELP protein or detecting a rearrangement in the genomic *elp* locus; wherein said mutation is located within the DNA region coding for the ENTH domain, in the 5' untranslated region, in a codon encoding an evolutionary conserved amino acid, in the promoter or in a splicing site; wherein said mutation leads to a non-functional ELP protein, to a reduced protein expression or no protein, or a fusion protein; wherein said nucleic acid sequence encoding an ELP protein is selected from the group consisting of SEQ ID NO: 1 or the nucleic acid sequence in claim 2; wherein the disease is lung cancer; wherein the disease is kidney cancer; wherein the disease is stomach cancer.

The specification at p. 6, lines 1-30 discloses that Applicants took a genetic approach in Drosophila to identify genes specifically involved in growth at a cellular, tissue, and organismal level. Specifically, they provided a genome-wide screen for recessive mutations that interfere or promote cell growth without affecting cell

proliferation. The screens were carried out on flies homozygous for randomly induced mutations in the head tissue but heterozygous for the same mutation in the body and the germ line. Applicants assert that mutations in genes whose products selectively promote growth (potential oncogenes) will produce flies with small heads (as in the instant invention) while mutations in genes whose products exert a growth inhibiting function (potential tumor suppressor genes) results in flies with larger than normal heads. Applicants assert that the validity of this screen to find genes involved in tumorogenesis is exemplified by the identification of mutations in Drosophila homologues of known oncogenes such as the Target of Rapamycin TOR, Myc, Ras causing a small-head phenotype and mutations in known tumor suppressor gene homologues like PTEN, LATS and TS1 causing a big head phenotype (Huang, Potter et al. 1999; Oldham, Motagne et al. 2000). Further, the specification at p. 35, line 33 – p. 36, line 22 (Example XI and Table 3) discloses ELP RNA expression in normal vs. tumor tissues. Here, reductions in human ELP mRNA expression compared with their respective normal tissues were observed in the majorities of lung, kidney, and stomach cancer samples.

Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of these methods recited in the claims. Applicants have not disclosed methods involving a change in the expression level of an ELP protein or at least one mutation within a nucleic acid sequence encoding an ELP protein or detecting a rearrangement in the genomic *elp* locus. Applicants have only disclosed methods involving measuring a downregulation of mRNA expression of hELP in lung, kidney, and

stomach cancer samples. No data is presented regarding the levels of protein expression. It does not necessarily follow that a decrease in copy number of the mRNA results in a change in protein expression that would correlate to the disease state. Haynes et al. (Electrophoresis 19: 1862-1871, 1998) studied 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein sand transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Haynes concluded that the protein levels couldn't be accurately predicted from the level of the corresponding mRNA transcript (page 1863, second paragraph and Figure 1). Further, these data are correlative only; there is no nexus established between reduced ELP mRNA expression and the development of a hyperproliferative disease.

Also, Applicants' genetic data in Drosophila showing that mutations in *elp* genes result in smaller head size are insufficient to establish a nexus between detecting any mutation in a nucleic acid sequence encoding an ELP protein or detecting a rearrangement in the genomic *elp* locus and the identification of a hyperproliferative disease. The assertion that mutations in other Drosophila homologues of known oncogenes causes a small head phenotype or in tumor suppressor gene homologues causes a large head phenotype cannot be accepted in the absence of supporting evidence, because relevant literature reports examples of growth factor families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular smooth

muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125: 1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family Vukicevic et al. (1996, PNAS USA 93: 9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2.) See also Massague, who reviews other members of the TGF-β family (1987, Cell 49: 437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et al. 1993, Bone 14: 717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) discloses several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the large quantity of experimentation necessary to establish a nexus between detecting a change in the expression level of an ELP protein, any mutation in a nucleic acid sequence encoding an ELP protein, or a rearrangement in the genomic *elp* locus and the identification of a hyperproliferative disease, given the lack of direction/guidance presented in the

specification, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claimed methods, and the breadth of the claims which encompass changes in protein expression and any mutation or rearrangement in nucleic acid expression, undue experimentation would be required of the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a selection step and a conclusion step.

The claims are drawn to a method for the identification of a hyperproliferative disease, in particular benign and malignant tumors, or a genetic predisposition thereof, which comprises detecting in a body fluid or a tissue sample of a subject a change in the expression level of an ELP protein or at least one mutation within a nucleic acid sequence encoding an ELP protein or detecting a rearrangement in the genomic *elp* locus. Applicant omitted the selection step for said subject. If the claim language was

amended to recite "a subject in need thereof" for example, the rejection may be reconsidered. Additionally, there is no conclusion for the recited method.

Conclusion

No claims are allowable.

References

The Office will no longer be supplying paper copies of U.S. Patents cited in Office Actions. Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Applicant may direct inquiries about the use of the Office's PAIR system to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached on Monday through Friday from 8:30AM to 5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gregory S. Emch, Ph. D.
Patent Examiner
Art Unit 1649
August 18, 2005

JOSEPH MURPHY
PATENT EXAMINER